REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

1. STATUS OF CLAIMS AND FORMAL MATTERS INCLUDING PRIORITY

The Examiner has alleged that the current pending claims are not entitled to the benefit of the priority date of May 12, 2000, and are instead entitled only to the date of filing the present application, October 30, 2003. Applicants maintain the position that the priority date of the present claims should be **May 12, 2000**, not October 30, 2003.

Claims 25-33 are under consideration in this application. All previous claims were cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Applicants reserve the right to pursue the subject matter of cancelled claims in continuing application.

No new matter has been added.

Support for the new claims is found throughout the specification, the original claims, and the new figures and examples. More in particular, support for claim 25 can be found for example at page 18, line 21 to page 19, line 25, page 22, line 11, Example 1, former claim 1, page 4, line 25, page 6, line 11, page 19, line 25, page 4, line 23, Example 6 at page 32, lines 20-24. Support for claim 26 can be found for example at page 4, line 25, page 18, line 15, page 19, line 27 to page 20 lines 1-3, Figures 33-35, Examples 10, 12-15, and in former claim 9. Support for claim 27 can be found for example at page 19, line 4, Example 2, Figure 3, and in former claims 6 and 7. Support for claim 28 can be found for example at page 6, line 27 to page 7 line 1, page 18, line 26, former claim 4. Support for claims 29 and 30 can be found in Examples 9 and 13 and in former claims 3, 4, 6, and 7. Support for claim 31 can be found for example at page 20, line 4, and in former claim 10. Support for claim 32 can be found for example at page 20, line 10, and in former claim 11. Support for claim 33 can be found for example in Example 4, page 29, lines 19-21 and in Figures 11 and 12.

It is respectfully submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are and were in

full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2. COMPLIANCE WITH SEQUENCE RULES

The Office Action notes that the Specification and Claims must be amended to be in compliance with the requirements for sequence listings under 37 C.F.R. § 1.821(d). It is respectfully submitted that the amendments herein have brought the Specification and Claims into compliance with the Sequence Rules. Accordingly, Applicants respectfully request that any objections based on the sequence listing requirements be reconsidered and withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ARE OVERCOME

Claims 1-24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In other words, claims 1-24 allegedly encompass subject matter which was not sufficiently described to convey to one of ordinary skill in the art that the invention was in the possession of the inventors.

The Office Action rejects claim 1 for allegedly lacking enablement on the basis that the specification fails to provide sufficient guidance teaching how to make or use a single adenoviral embodiment whose replication is limited to a "specific" cell type. It further alleges that there are no working examples describing an adenovirus exhibiting both redirected tropism and conditional early gene-mediated cell type-specific replication in the cell to which the redirected tropism is directed that would limit replication of the CRAd to a specific cell type. The Office Action alleges that in order to meet the limitations of claim 1 drawn to an adenovirus whose replication is limited to a specific cell type, the specification would have to provide sufficient guidance for making and using an adenovirus with a CAR-ablated phenotype, a new cell type-specific tropism, and/or a selective ability to replicate in one specific cell type to the exclusion of all others. The claims have been amended, rendering this objection moot.

The presently claimed invention is no longer limited to a "specific" cell type. Rather, claim 25 teaches a conditionally replicative adenovirus which directs entry of the CRAd into

tumor cells more efficiently than an identical conditionally replicative adenovirus comprising a wild-type fiber protein, and which comprises a tumor-specific promoter operably linked to one or more early genes selected from the group consisting of E1, E2, and E4.

The Office Action furthermore alleges that the specification provides virtually no guidance concerning the specific nature of any ligands for use in the claimed methods or compositions selected from the group consisting of physiological ligands, anti-receptor antibodies, or cell-specific peptides, nor does it provide guidance concerning structural constraints which limit the extent to which ligands can be introduced into the HI loop so as to maintain a structurally appropriate functional fiber trimer capable of mediating capsid assembly into functional and mature viral particles. It alleges that the prior art as taught by Curiel and Dmitriev reveal that the full scope of the claimed embodiments were not enabled at the time the invention was made and that the specification provides insufficient guidance or predictability for making and using the claimed embodiments.

The Office Action also alleges that the specification proposes to design adenoviruses containing artificial non-fiber substitute proteins for redirected cell tropism, but fails to provide specific guidance on how to make or design redirected adenoviruses carrying such artificial proteins, nor does it provide a predictable basis for making such functional adenovirus embodiments in the absence of undue experimentation, give that this has not been done before and given the uncertainty concerning structural constraints and/or size restrictions associated with maintenance of an appropriate trimerized structure capable of assembling into a functional viral particle that can enter and translocate to the nucleus.

The Office Action alleges the specification does not sufficiently teach which targeting domains can be incorporated into the claimed compositions so as to preserve the targeting, infectability, nuclear translocation, and replication of cells. Furthermore, the specification does not provide any *a priori* basis for determining which targeting ligands or substitute proteins would facilitate proper assembly of functional adenovirus particles for use in the claimed methods.

The Office Action alleges that the specification further fails to provide a sufficiently enabling disclosure teaching how to make CRAds whose replication is limited to any specific cell type based upon a "conditionally-regulated early gene."

The rejection is respectfully traversed for the following reasons.

It is respectfully asserted that the state of the art pertaining to the invention was not unpredictable at the time of filing the application and thus could have been relied on for guidance in practicing the claimed invention. Techniques for the modification of the HI loop of the fiber knob were well known to one of ordinary sill in the art. In fact, as the Office Action points out, Dmitriev demonstrated that recombinant Ad vector containing fibers with RGD motif (which has affinity for tumor vasculature, as demonstrated by Pasqualini) in the HI loop is capable of dramatically augmenting gene delivery to target cells via a CAR-independent cell entry mechanism. This is precisely the same peptide used in Examples 2, 3, 6, 7 8 of the instant specification and recited in claim 30.

Moreover, independent claim 25 presently recites incorporation of a ligand, specifically either an Arg-Gly-Asp (RGD)-containing peptide in the HI loop of the fiber knob domain or, the modified conditionally replicative adenovirus containing a fiber knob domain from a different subtype of adenovirus. This alleviates Examiner's concern regarding the specific nature of the ligands used as substitute in the HI loop of the fiber knob domain or as substitute for the fiber knob. Furthermore, Example 2 teaches incorporation of the RGD peptide into the fiber of the Ad5lucRGD adenoviral vector. Example 3 teaches enhanced infectivity, over unmodified vectors, of tumors after incorporation of RGD sequence into the HI loop of the fiber. Example 8 teaches that introduction of an RGD sequence in the fiber of a CRAd allows CAR-independent infection that leads to the enhancement of viral propagation and oncolytic effect *in vitro* and *in vivo*. These Examples serve to alleviate any concerns regarding structural constraints as well as maintaining a functional fiber trimer capable of mediating capsid assembly into functional and mature viral particles.

In summary, all of these modifications obviate the rejection since they clearly convey that the present invention is indeed enabled. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, are respectfully requested.

4. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, ARE OVERCOME

Claim 16 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is allegedly insufficient antecedent basis for the limitation of

"said cell" in the claims. Claim 16 has been cancelled, thereby rendering the objection moot. The present claim set nowhere recites the limitation "said cell".

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

5. THE REJECTIONS UNDER 35 U.S.C. § 102 ARE OVERCOME

Claims 1-5, 8, 9, 13, 15-19, 22 and 23 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Takayama et al., (Mol. Ther. 7(5, Part 2): S420, abstract 1089) as evidenced by Curiel et al., WO 00/67576.

It is submitted that Takayama *et al.* is not a prior art document. Attached hereto is a Declaration under 35 C.F.R. §1.132 (hereinafter "Declaration"). The Declaration is presently signed by David T. Curiel and Igor Dmitriev, and unsigned by Victor Krasnykh and Ramon Alemany. A Declaration signed by all inventors will be provided. The Declaration filed December 22, 2005 states that Takayama *et al.* is not the work of others as defined by 35 U.S.C. §102(a). The Declaration is sufficient to overcome the grounds of rejection of claims 1-5, 8, 9, 13, 15-19, 22 and 23 under 35 U.S.C. § 102(a) because the Declaration clearly states that K. Takayama, J. Uchino, A. Ikegami, P.N. Reynolds, Y. Adachi, L. Kaliberova did not make an independent inventive contribution to the invention claimed in this application. Should the rejection be maintained, the Examiner is requested to indicate how the Declaration fails to successfully overcome the grounds of rejection.

Claims 1-5, 8-10, 13, 15-19, and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002)as evidenced by Curiel et al., WO 00/67576.

It is submitted that Curiel is not a prior art document. The Declaration Under 37 C.F.R. § 1.132 (hereinafter "Declaration") filed December 22, 2005 states that Curiel is not the work of others as defined by 35 U.S.C. §102(a). The Declaration is presently signed by David T. Curiel and Igor Dmitriev, and unsigned by Victor Krasnykh and Ramon Alemany. A Declaration signed by all inventors will be provided. The Declaration is sufficient to overcome the grounds of rejection of claims 1-5, 8-10, 13, 15-19, and 22-24 under 35 U.S.C. § 102(a) because the Declaration clearly states that D.T. Curiel is the only author of Curiel and has also made an independent inventive contribution to the invention claimed in this application. Should the

rejection be maintained, the Examiner is requested to indicate how the Declaration fails to successfully overcome the grounds of rejection.

Claims 1-4 and 8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stevenson et al. (J. Virol., 71(6): 4782-4790, June 1997), as evidenced by Imler et al. (Gene Ther. 3: 75-84, 1996) with respect to claim 2.

Claims 1-8, 10-22, and 24 are rejected under 35 U.S.C. § 102(b) & (e) as being anticipated by Wickham et al. (U.S. 5,846,782, issued 12/8/99). These two rejections are respectfully traversed and dealt with collectively.

MPEP 2131 states in part that "A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)." For a proper anticipation rejection, the reference "must ***clearly and unequivocally disclose*** the claimed compound or direct those skilled in the art to the compound ***without any need for picking, choosing***, and combining various disclosures not directly related to each other by the teachings of the cited reference." See *In re Arkley*, 455 F.2d 586, 587, 172 USPQ 524, 526 (CCPA 1972) (emphasis added). None of the above prior art references meet this standard.

Furthermore, it is respectfully asserted that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Stevenson relates to an infectivity-enhanced conditionally replicative adenovirus possessing enhanced infectivity towards specific clinically relevant target tissues as compared to wild-type Ad5 due to replacement of the Ad5 fiber head domain comprising an HI loop with a homologous Ad3 fiber head domain wherein said infectivity-enhanced conditionally-replicative adenovirus has conditionally regulated E2 and E4 gene carrying their endogenous promoters

directing conditional expression and replication of said adenovirus to specific cells which carry E1 gene products in trans.

Wickham relates to an infectivity-enhanced conditionally replicative adenovirus possessing enhanced infectivity towards a specific cell type relative to wild-type adenovirus due to introduction of an RGD peptide into the HI loop of the fiber, further comprising at least three conditionally regulated early genes such that replication is limited to cells providing E1 gene products in trans. Further, Wickham relates to adenoviral vectors that carry a therapeutic gene exerting its therapeutic effect through expression of a HSV thymidine kinase gene rendering cells selectively sensitive to the killing action of gancyclovir, and using such vectors to treat cancer.

Claims 1-24 have been cancelled. Claims 26-33 depend from claim 25. Claim 25 is drawn to a conditional replication-enabling system comprising an infectivity-enhanced conditionally replicative adenovirus (CRAd). Furthermore, the CRAd of claim 25 contains a modified fiber protein wherein it contains and expresses a nucleotide sequence encoding the ligand, and wherein the ligand comprises Arg-Gly-Asp in the HI loop of the fiber. Alternatively, the CRAd contains a fiber knob domain from a different subtype of adenovirus. In both instances, the ligand, or fiber knob domain, provides a pathway to cell binding by the modified CRAd other than the coxsackie-adenovirus receptor, and thereby enhances infectivity of the conditionally replicative adenovirus in tumor cells over that of wild-type adenovirus. Furthermore, the CRAd of claim 25 encodes a tumor-specific promoter operably linked to one or more early genes selected from the group consisting of E1, E2 and E4. As amended, the claims are limited to unequivocally exclude what are generally called replication-defective adenovirus. Independent claim 25 is limited to conditional regulation due to a tumor-specific promoter operably linked to one or more early genes selected from the group consisting of E1, E2, and E4. Claim 26 teaches conditional replication of the adenovirus of claim 25 due to insertion of a specific tumor promoter gene encoding a protein selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 and surviving. Neither Stevenson nor Wickham relate to conditional regulation due to these disclosed tumor-specific promoters. Therefore, these portions of the rejection can be properly withdrawn.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §102 are respectfully requested.

6. THE 35 U.S.C. § 103(a) REJECTIONS HAVE BEEN OVERCOME

Claims 1, 4, 6, 7, 10-14, 18, 20, 21 and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Takayama et al. (Mol. Ther. 7(5, Part 2): S420, abstract 1089) in view of Curiel et al. WO 00/67576.

Claims 1, 4, 6, 7, 10-14, 18, 20, 21 and 24 are also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Curiel, D. T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663 abstract 3287, March 2002) in view of Curiel et al., WO 00/67576.

Claims 1-24 are further rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Molnar-Kimber, WO 01/23004 in view of Curiel et al., WO 00/67576.

It is submitted that Takayama *et al.* is not a prior art document. The Declaration Under 37 C.F.R. § 1.132 (hereinafter "Declaration") filed December 22, 2005 states that Takayama *et al.* is not the work of others as defined by 35 U.S.C. §102(a). The Declaration is sufficient to overcome the grounds of rejection of claims 1-5, 8, 9, 13, 15-19, 22 and 23 under 35 U.S.C. § 103(a) because the Declaration clearly states that K. Takayama, J. Uchino, A. Ikegami, P.N. Reynolds, Y. Adachi, L. Kaliberova did not make an independent inventive contribution to the invention claimed in this application. Should the rejection be maintained, the Examiner is requested to indicate how the Declaration fails to successfully overcome the grounds of rejection.

It is submitted that Curiel is not a prior art document. The Declaration Under 37 C.F.R. § 1.132 (hereinafter "Declaration") filed December 22, 2005 states that Curiel is not the work of others as defined by 35 U.S.C. §102(a). The Declaration is sufficient to overcome the grounds of rejection of claims 1-5, 8-10, 13, 15-19, and 22-24 under 35 U.S.C. § 103(a) because the Declaration clearly states that D.T. Curiel is the only author of Curiel and has also made an independent inventive contribution to the invention claimed in this application. Should the rejection be maintained, the Examiner is requested to indicate how the Declaration fails to successfully overcome the grounds of rejection.

The rejection is respectfully traversed for the following reasons.

While the applicants do not concede that the claims are obvious, this issue is moot as applicants believe Takayama and Curiel have been disqualified as prior art under 35 U.S.C. §103(c) as established by the Katz declarations.

Moreover, it is respectfully submitted that it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further still, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Molnar-Kimber relates to CRAds and methods of using the CRAds for the treatment of cancer. The CRAds comprise an E1A gene under control of a tumor specific promoter, such as the surviving promoter to render the CRAd conditionally replicative in tumor cells. The CRAd may also contain a therapeutic gene encoding HSV tk to augment the oncolytic activity, where gancyclovir is also administered. However, Molnar-Kimber does not teach or suggest to modify the adenoviral fiber either by insertion of an RGD peptide into the HI loop or by replacing the knob with that of a different adenovirus. Therefore, for the foregoing reasons it would not have been obvious to one of skill in the art at the time the invention was made to have modified the fiber of the CRAd of Molnar-Kimber by insertion of an RGD peptide into the HI loop or by replacement of the fiber knob with that of a different adenovirus, with any expectation of success.

Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

7. THE DOUBLE PATENTING REJECTIONS ARE OVERCOME

Claims 1-8, 10-22 and 24 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-12 of U.S. Patent No. 6,824,771.

The issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to the '771 patent will be filed for the purposes of expediting prosecution.

Claims 1-8, 10-22 and 24 are also rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-4, 9, 11, 16, 22, 23 and 26-29 of copending Application No. 09/245,603.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

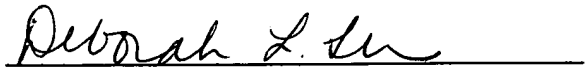
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner is respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks, amendments and Declaration, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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